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1
ACCESSION NUMBER: 2001336287 MEDLINE
TITLE: Pyruvate/dichloroacetate supply during reperfusion accelerates recovery of cardiac energetics and improves mechanical function following cardioplegic arrest.
AUTHOR: Smolenski R T; Amrani M; Jayakumar J; Jagodzinski P; Gray C C; Goodwin A T; Sammut I A; Yacoub M H
SOURCE: EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, (2001 Jun) 19 (6) 865-72.

2

ACCESSION NUMBER: 2002121773 MEDLINE
TITLE: Energetic stimulation of the heart
AUTHOR: Hermann H P
SOURCE: CARDIOVASCULAR DRUGS AND THERAPY, (2001 Sep) 15 (5) 405-11.

3.
ACCESSION NUMBER: 85239005 MEDLINE
TITLE: The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation.
AUTHOR: McKnight C K; Elliott M J; Pearson D T; Holden M P; Alberti K G
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1985 Jul) 90 (1) 97-111

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SYMPOSIUM: NOVEL INOTROPIC MECHANISMS—A NEW HORIZON FOR HEART FAILURE

Energetic Stimulation of the Heart

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Summary. **The management of patients with acute heart failure includes frequently the use of positive inotropic agents in order to increase cardiac output and hence to maintain adequate tissue perfusion. The concept of energetic stimulation of the heart was invented in order to avoid deleterious effects of conventional inotropes, i.e. catecholamines and phosphodiesterase-inhibitors, on myocardial oxygen consumption and energy reserves and to circumvent potential dangerous side effects of the drugs. Metabolic support with glucose-insulin-potassium has proven efficious of improving cardiac performance and prognosis in the setting of the ischemic and postischemic heart. The glycolytic intermediate pyruvate increases contractile performance in isolated animal and human myocardium and improves short-time hemodynamics in patients with congestive heart failure, which is discussed in detail in the present article. Energetic stimulation with pyruvate could therefore be a new promising approach to the treatment of acute heart failure, if conventional therapy fails.**

Key Words. **heart failure, pyruvate, glucose-insulin-potassium, inotropic agents, calcium**

History of Metabolic Support for the Heart

The first description of a treatment of heart failure with west indian cane sugar is dated on 1912 and was published by the British physician Goulston [1]. He analyzed radial pulse tracings before and after sugar ingestion in heart failure patients. The idea of a nutritional treatment of the heart muscle with intravenous glucose was invented at about the same time by Büdingen in Germany [2]. The concept of metabolic support for the failing heart was transferred to the issue of the ischemic heart and myocardial infarction by Sodi-Pallares in the middle of the 20th century [3]. He treated patients with arrhythmias during acute myocardial infarction with a solution containing glucose, insulin and potassium and termed this a "polarizing solution" which should activate sarcolemmal Na^+/K^+-ATPase to prevent intracellular potassium loss and therefore decrease electrical instability of the infarcted myocardium. To test this hypothesis, a controlled clinical trial was performed by the British Medical Research Council which failed to demonstrate any survival benefit of a glucose–insulin–potassium solution and the concept of metabolic support was put to rest [4].

Glucose–Insulin–Potassium (GIK)

It was the merit of Taegtmeyer and Gradinak in Houston in the late 1980s to recognize the therapeutic impact of metabolic support/energetic stimulation of the heart by objective measurement of hemodynamic and clinical parameters in patients with low output failure following coronary artery bypass surgery. They assigned patients with refractory left ventricular failure after cardiopulmonary bypass for CABG-surgery to a regimen consisting of intra-aortic balloon counterpulsation (IABP) plus either intravenous inotropic drugs (control) or inotropic drugs with glucose–insulin–potassium-infusion (GIK) for the first 48 h after surgery [5,6]. The study showed a favorable outcome of patients with GIK-therapy with shorter duration on intraaortic balloon counterpulsation and reduced mortality. These results formed the basis for larger randomized studies on GIK-therapy in acute myocardial infarction which opposed the earlier data of the British Medical Research Council: Malmberg and colleagues found in the prospective DIGAMI trial a 29% mortality reduction of diabetic patients with acute myocardial infarction receiving a insulin–glucose infusion followed by subcutaneous insulin treatment for at least 3 months [7]. This mortality reduction was particularily evident in patients with a low cardiovascular risk profile and no previous insulin treatment with a relative risk reduction of 52%.

According to the results of the DIGAMI study in diabetic patients, Fath-Ordoubadi and Beatt found in a meta-analysis of 9 randomized. placebo-controlled trials including a total of 1932 patients with acute myocardial infarction a mortality reduction of 28% with glucose–insulin–potassium therapy [8]. The first large randomized trial in the thrombolytic era, the South American ECLA trial by Díaz and coworkers, recently

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confirmed these findings: 407 patients with acute myocardial infarction were allocated to receive a 24 h GIK-infusion (high- or low-dose) or control [9]. In patients treated with reperfusion strategies, the authors found a significant 66% reduction in mortality during hospitalization which could be mainly attributed to reduced incidence of severe heart failure and ventricular fibrillation.

The therapeutic benefit of the glucose–insulin-infusion in myocardial infarction may be attributed to an inhibition of fatty acid metabolism with a reduction of circulating free fatty acids and metabolites and to an improvement of impaired substrate supply in low flow ischemia or infarction which hinges on the fact that glucose can be metabolized anaerobically and can thereby provide glycolytic ATP in the cytosolic compartment. This is in accordance with data from Oliver and Opie who showed in ischemic myocardium deleterious effects of high circulating free fatty acid (FFA) concentrations on myocardial function and arrhythmogenesis produced by endogenous catecholamine stimulation [10]. High FFA lead to increased myocardial oxygen requirement, may cause impaired calcium homeostasis and production of free radicals ultimately leading to electrical instability and depression of contractility. The enhanced free fatty acid oxidation may be effectively suppressed by insulin–glucose infusion with substrate support of glycolysis, this may be of particular importance for the maintenance of membrane function and hence cytosolic calcium- and sodium homeostasis. Additional effects of glucose–insulin treatment include a restoration of impaired platelet function, correction of a disturbed lipoprotein pattern and a decrease in plasminogen activator–inhibitor-1 activity (PAI-1) which is elevated in diabetic patients. Several recent trials including DIGAMI support complementary roles of GIK and reperfusion therapy. Furthermore, glucose metabolism provides additional substrate for the tricarboxylic acid cycle which enhances cycle flux through generation of pyruvate and leads during reperfusion to aerobically produced ATP.

However, so far no positive inotropic effects of GIK could be demonstrated in isolated healthy or failing myocardium of non-ischemic etiology.

Amino Acids: Glutamate and Aspartate

Under normal aerobic conditions and normal substrate supply, amino acid oxidation accounts for less than 5% of myocardial energy production. L-glutamate is the only amino acid that is substantially metabolized by normal myocardium. During ischemia and reperfusion, glutamate and aspartate may become preferred fuels and their tissue levels fall, while alanine is generated. In ischemic and stunned animal myocardium several studies have shown beneficial effects of a high-dose glutamate infusion [11,12]. Glutamate-enriched or α-ketoglutarate-enriched cardioplegic solutions resulted in moderately improved hemodynamics in patients undergoing coronary bypass surgery and a combination of glutamate and GIK was successful in treatment of postoperative low-output failure oder cardiogenic shock after CABG [13–15].

Postulated mechanisms of action of amino acid supplementation with glutamate include an activation of the malate–aspartate–shuttle with translocation of reducing equivalents (NADH) from the cytoplasm into the mitochondrial matrix where they enter the respiratory chain generating ATP. Furthermore, glutamate may be transaminated to form α-ketoglutarate which can directly enter the citric acid cycle [16]. The hemodynamic effects of amino acid infusions seem in general to be moderate and may be attributed to indirect substrate substitution of citric acid cycle intermediates via transamination.

Pyruvate: Salt of Pyruvic Acid

Pyruvate is formed as an intermediate of glycolysis and represents an excellent energy-yielding substrate for mammalian hearts. After recognition of its key role in oxidative energy metabolism by Krebs and Johnson [17], pyruvate was first-time used as a substrate in isolated heart-lung preparations by Braun-Menendez and Chute in 1939 [18]. The importance of pyruvate as a substrate for the failing heart was recognized by Bünger and coworkers in late 1970s who systematically investigated isolated Langendorff heart preparations perfused with pyruvate [19]. They found significant positive inotropic effects predominantly in ischemic damaged myocardium, i.e. "stunned" myocardium where exogenous pyruvate could prevent postischemic or reperfusion contractile failure [20]. Experimental findings have recently shown that exogenous pyruvate exerts positive-inotropic effects and improves contractile function *in vivo* in healthy and diseased (hypoxic or postischemic) canine and swine hearts [21–24], *in vitro* in perfused rabbit hearts [25], in isolated rat myocytes [26] and in isolated multicellular muscle preparations from rabbit myocardium [27].

Therefore we decided to investigate the effects of pyruvate on hemodynamics and clinical parameters in patients with congestive heart failure and to characterize the subcellular action mechanisms of pyruvate with particular respect to calcium handling of the myocardium.

The clinical study was performed in 8 consecutive patients during diagnostic cardiac catheterization for cardiomyopathy of unknown etiology. Patients were included if left ventricular ejection fraction was below 25%, and cardiac index was below 2.5 l/min/m^2 or pulmonary capillary wedge pressure was above 15 mm Hg, all patients were in NYHA functional class III.

Cardiac catheterization was performed from the right femoral artery and vein with all medication having been withheld for 12 hours. After coronary artery and valvular disease had been excluded, a pulmonary artery-catheter was placed and a 5 F left coronary

artery catheter was advanced to the left main coronary artery. Approximately 30 min after coronary angiography, baseline measurements of hemodynamics were performed. Thereafter, infusion of pyruvate (150 mmol/l) was started at 370 ml/hour. Assuming a coronary blood flow of 300 ml/min this would result in a coronary arterial pyruvate concentration of approximately 3 mmol/l. After 15 min measurements were repeated and thereafter, pyruvate infusion rate was increased to 740 ml/min for another 15 min with subsequent hemodynamic measurements. Intracoronary infusion of pyruvate was followed by 15 min washout of intracoronary saline infusion (0.9%, 370 ml/hour) with subsequent hemodynamic measurements.

Pyruvate increased stroke volume index and decreased pulmonary capillary wedge pressure in each individual patient with dilated cardiomyopathy. Compared to baseline, pyruvate increased stroke volume index by 38% (Fig. 1) and decreased pulmonary capillary wedge pressure by 36% (Fig. 2). The positive inotropic effect of pyruvate was associated with a decrease in heart rate by 11% (Fig. 3), whereas cardiac index increased by 23%. Pyruvate reduced mean pulmonary artery pressure and pulmonary vascular resistance by 26% and 28%, respectively. Systolic aortic pressure increased slightly by 8%, whereas mean aortic pressure and systemic vascular resistance did not change (Fig. 4). No side effects of the pyruvate infusion were observed. Substitution of pyruvate by intracoronary infusion of saline resulted in reversal of its hemodynamic effects of all parameters within 15 minutes besides diastolic pulmonary artery pressure and mean right atrial pressure, which were increased by 31% and 20%, respectively, compared to baseline [28].

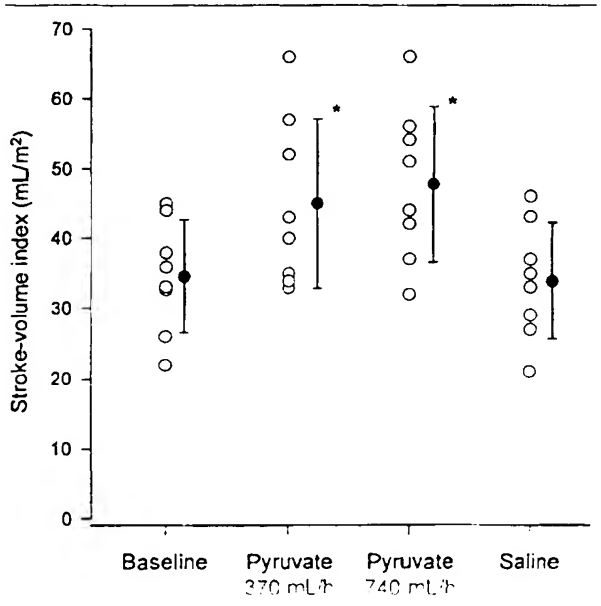

*Fig. 1. Influence of different pyruvate concentrations on stroke volume index. *p < 0.05 vs. baseline and saline.*

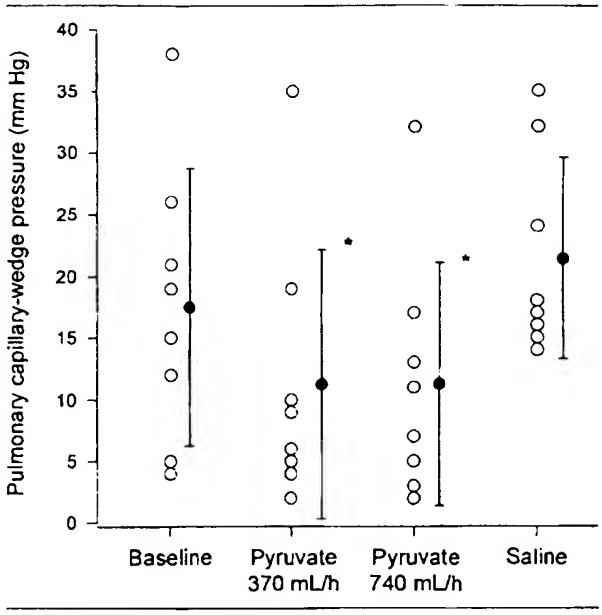

Fig. 2. *Influence of different pyruvate concentrations on pulmonary capillary wedge pressure. *p < 0.05 vs. baseline and saline.*

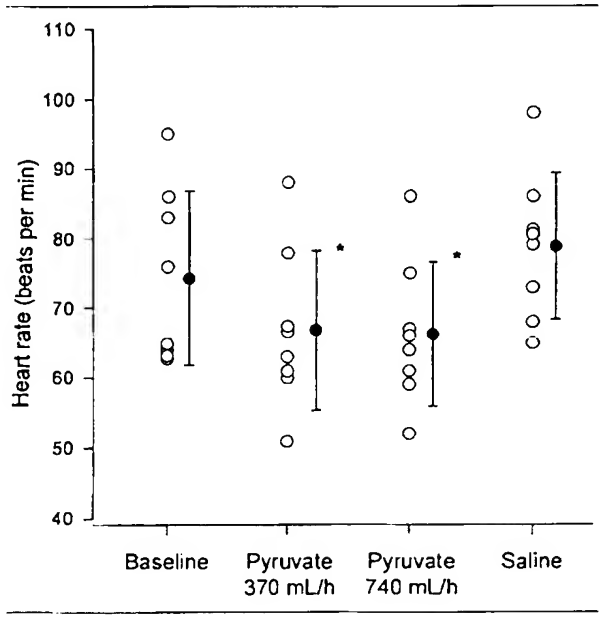

Fig. 3. *Influence of different pyruvate concentrations on heart rate. *p < 0.05 vs. baseline and saline.*

The increase in cardiac index following intracoronary infusion of pyruvate occured despite a decrease in heart rate due to a pronounced increase in stroke volume index. In addition, pulmonary capillary wedge pressure decreased considerably. These hemodynamic effects resulted most likely from direct pyruvate actions on the myocardium because (1) systemic pyruvate

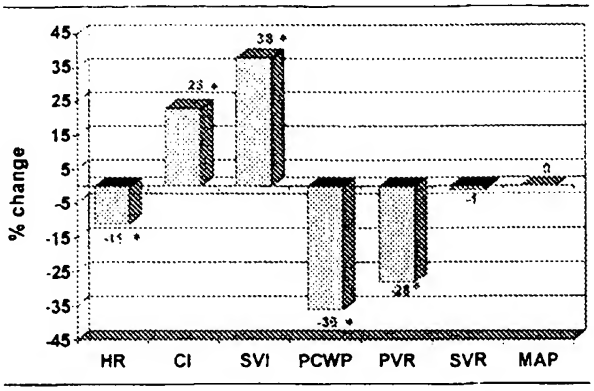

*Fig. 4. Influence of pyruvate (240 ml/h) on hemodynamic parameters. HR, heart rate; CI, cardiac index; SVI, stroke volume index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; MAP, mean aortic pressure. *$p < 0.05$ vs. baseline and saline.*

levels did not significantly increase, (2) mean arterial pressure and systemic vascular resistance did not significantly change and (3) previous studies showed that pyruvate does not induce coronary vasodilation. In contrast to catecholamines and phosphodiesterase inhibitors, the inotropic effect of pyruvate was associated with a significant decrease in heart rate. This may have resulted from augmented baroreceptor reflex inhibition of sympathetic tone following an increase in stroke volume or from decreased sympathetic tone due to improvement of the metabolic situation of the myocardium.

The experimental study was carried out in isolated multicellular muscle preparations from end-stage failing human hearts which were obtained from explanted hearts of patients undergoing heart transplantation. Isometric contractions were elicited in muscle chambers at 37°C and 1 Hz stimulation frequency. Twitch force, rates of force rise and fall and twitch timing parameters were obtained from on-line registration of digitized data. Isometric force signals were recorded under baseline condition and after application of different pyruvate concentrations. To investigate cytosolic calcium transients, in a separate series of experiments the calcium-regulated bioluminescent photoprotein aequorin was injected into the muscle preparations and the aequorin light signal during isometric contractions was measured. The amplitude of the aequorin light signal reflects cytosolic calcium transients. Finally, sarcoplasmic reticulum calcium content was analyzed using rapid cooling contractures (RCCs). Instantaneous cooling of the multicellular preparations in the organ bath from 37°C to 1°C within 1–2 seconds with customized heat–cold exchangers leads to a near-complete calcium release from the sarcoplasmic reticulum (SR) and a stable contracture develops. The amplitude of the cooling contracture reflects mainly the calcium content of the SR.

Addition of pyruvate (20 mM) resulted in a dose-dependent increase in systolic force and decrease in diastolic force by 155% and 21% respectively. This was associated with increased time to peak tension and time to 50% relaxation. The inotropic effect was associated with a pronounced increase in aequorin light signals indicating increased calcium transients. Interestingly, the increase in light signal was smaller after pyruvate application compared to the signal of equivalent force generation with isoproterenol stimulation, i.e. calcium cycling was more efficient with pyruvate. The rapid cooling experiments revealed increased amplitude of cooling contractures reflecting augmented SR calcium content with pyruvate application.

In light of these results we investigated in a subsequent study the effects of a combination of pyruvate and the β-adrenergic agonist isoproterenol or increased extracellular calcium on inotropic response and calcium cycling [27]. This study was performed in isolated non-failing rabbit myocardium and the rationale was to detect additive effects of pyruvate and catecholamines which might be of clinical importance in the setting of acute heart failure in order to circumvent deleterious effects on energy demand during catecholamine application.

The combination of pyruvate (10 mM) and isoproterenol (10^{-6} M) exhibited not only additive but also potentiating effects on isometric force generation, i.e. in presence of pyruvate, isoproterenol induced larger increases in inotropy than could be calculated by mere addition of the individual inotropic effects (Fig. 5). At concentrations of isoproterenol (10^{-6} M) or calcium (16 mM) that alone produced maximal increases of isometric force, pyruvate (10 mM) was able to further increase developed force. In addition, pyruvate further increased SR calcium load at saturating extracellular calcium concentrations (16 mM). The potentiating inotropic effect of pyruvate may therefore result from (a) stimulation of SR calcium accumulation with subsequent increased SR calcium release, (b) increased myofilament sensitivity and (c) alterations in cross-bridge kinetics.

Pyruvate exhibits numerous molecular effects which may contribute to its inotropic action. These include a reduction of inorganic phosphate, a modulation of intracellular pH and cytosolic redox state [20,25,29,30] as well as antioxidative effects [31–33]. However, the most important mechanism for the inotropic and lusitropic effect may be an improvement of myocardial energetics with increased phosphorylation potential and a subsequent increase of the thermodynamic driving force for the sarcoplasmic reticulum (SR) calcium pump [34,35]. Accordingly, it was recently shown that pyruvate increases the free energy from ATP-hydrolysis which is associated with an accentuation of the SR-calcium gradient [34]. Increased SR calcium accumulation will result in augmented calcium release with increased calcium activation of contractile proteins and thus improved systolic performance as well as in reduced

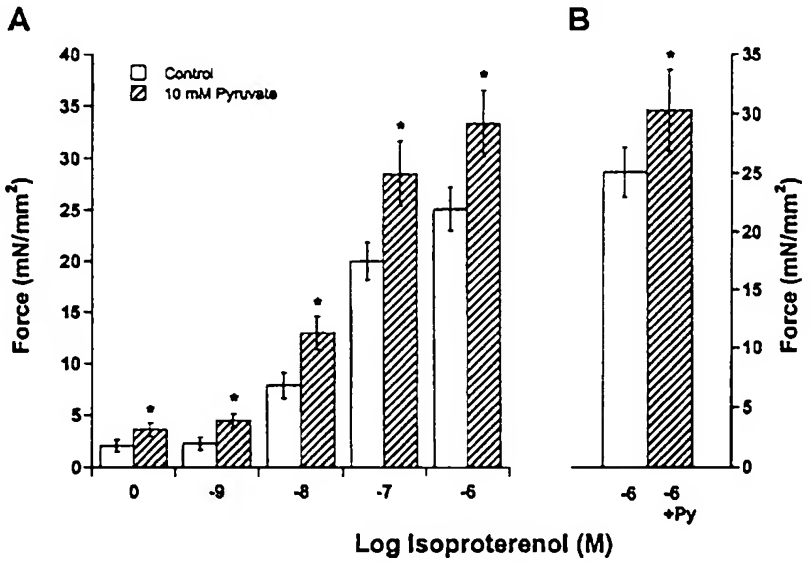

*Fig. 5. Potentiating effect of pyruvate on isoproterenol-induced positive inotropy. A: average data of developed force during an isoproterenol concentration–response curve before and after addition of 10 mM pyruvate at 1.25 mM Ca^{2+} (n = 8). The isoproterenol response in presence of pyruvate was significantly potentiated at all concentrations, i.e. the isoproterenol induced increase in force development was larger in presence of pyruvate. B: under saturating isoproterenol concentrations (10^{-6}–10^{-5} M), 10 mM pyruvate could further increase force development. * denotes a significant ($p < 0.05$) increase compared to the same data in absence of pyruvate.*

diastolic calcium levels with improved diastolic function [26]. The effects of pyruvate on SR calcium pump are of particular interest because reduced SR calcium uptake seems to have a pivotal role in the pathophysiology of human heart failure [36–38].

The energetic effects of pyruvate result from its input into the tricarboxylic acid cycle (Krebs cycle): (1) Pyruvate enters the Krebs cycle as a substrate following decarboxylation by pyruvate dehydrogenase, (2) pyruvate enriches the Krebs cycle following carboxylation to oxaloacetate and malate (Fig. 6). The latter anaplerotic pathway increases flux through the Krebs cycle supplementing oxidative phosphorylation.

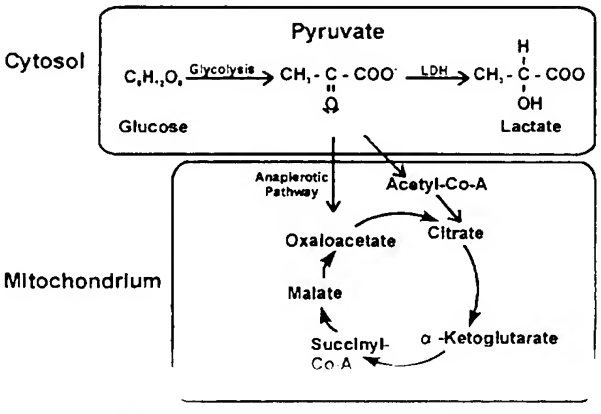

Fig. 6. Role of pyruvate in energy metabolism.

These energetic effects seem to be rather specific to pyruvate because administration of other substrates did not achieve similar energetic changes [20]. However, it should be mentioned that the beneficial action of glucose–insulin–potassium (GIK) in patients with myocardial infarction may be partially explained by increased glycolytic flux with increased generation of pyruvate [8,9].

Clinical Implications

Metabolic interventions to improve myocardial energetics may represent an important, previously unrecognized therapeutic option to improve hemodynamics in patients with heart failure. Intracoronary application of pyruvate may therefore be a novel approach to treat patients with acute heart failure and cardiogenic shock if conventional inotropic therapy fails and access to the coronary circulation is readily available. A combination of catecholamines with pyruvate may create a more effective inotropic therapy and could allow reduced catecholamine doses without attenuating therapeutic efficacy. The energetic effects of pyruvate may be of particular relevance in failing hearts, assuming that energy starvation contributes to myocardial failure [39].

Further studies are warranted to evaluate whether intravenous application of pyruvate at concentrations higher than those used in the present study may result in therapeutic plasma levels allowing intravenous

inotropic treatment of patients with congestive heart failure.

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